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MORRISON & FOERSTER LLP 755 PAGE MILL RD PALO ALTO, CA 94304-1018				MOORE, WILLIAM W
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	09/884,455	HOUGHTON ET AL.
	<b>Examiner</b>	<b>Art Unit</b>
	WILLIAM W. MOORE	1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 15 May 2008.

2a) This action is **FINAL**.                            2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 27-36 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 27-36 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.

    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All    b) Some \* c) None of:

- Certified copies of the priority documents have been received.
- Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
- Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.

4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.

5) Notice of Informal Patent Application

6) Other: \_\_\_\_\_.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 15 May 2008 has been entered. No claims were canceled or amended, and claims 27-36 remain in the application.

### *Double Patenting: Non-Statutory*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 27-30 remain rejected for reasons of record under the judicially created doctrine of obviousness- type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,585,258. Although page 2 of the Response indicates that Applicant will file a terminal disclaimer upon indication of allowable subject matter herein, the rejection must be maintained until and unless an effective terminal disclaimer is filed.

Claims 31-35 remain rejected for reasons of record under the judicially created doctrine of obviousness- type double patenting as being unpatentable over claims 5-9 of U.S. Patent No. 5,585,258 in view of Benson et al., U.S Patent No. 5,258,496. Although page 2 of the Response indicates that Applicant will file a terminal disclaimer upon indication of allowable subject matter herein, the rejection must be maintained until and unless an effective terminal disclaimer is filed.

Claim 36 remains rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3-5 of U.S. Patent No. 5,597,691. Although page 2 of the Response indicates that Applicant will file a terminal disclaimer upon indication of allowable subject matter herein, the rejection must be maintained until and unless an effective terminal disclaimer is filed.

Claims 27 and 30 remain rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 5,712,145. Although page 2 of the Response indicates that Applicant will file a terminal disclaimer upon indication of allowable subject matter herein, the rejection must be maintained until and unless an effective terminal disclaimer is filed.

Claims 31, 32 and 35 remain rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-5 of U.S. Patent No. 5,712,145 in view of Benson et al., U.S Patent No. 5,258,496. Although page 2 of the Response indicates that Applicant will file a terminal disclaimer upon indication of allowable subject matter herein, the rejection must be maintained until and unless an effective terminal disclaimer is filed.

Claim 36 remains rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7 and 8 of U.S. Patent No. 5,712,145. Although page 2 of the Response indicates that Applicant will file a terminal disclaimer upon indication of allowable subject matter herein, the rejection must be maintained until and unless an effective terminal disclaimer is filed.

The following are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Claims 27 and 30 remain provisionally rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 11 of copending Application No. 10/409,094, an application for reissue of U.S. Patent No. 5,585,258. Although page 3 of the Response indicates that Applicant will file a terminal disclaimer upon indication of allowable subject matter herein, the rejection must be maintained until and unless an effective terminal disclaimer is filed.

Claim 36 remains provisionally rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6 of copending Application No. 10/409,673, an application for reissue of U.S. Patent No. 5,597,691. Although page 3 of the Response indicates that Applicant will file a terminal disclaimer upon indication of allowable subject matter herein, the rejection must be maintained until and unless an effective terminal disclaimer is filed.

#### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-36 remain rejected for reasons of record under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant's arguments at pages 3-14 of the Response have been fully considered but are not deemed to be persuasive to overcome the rejection of record. Applicant now requests, at pages 15 and 15 of the Response, an affidavit under 37 CFR 1.104(d)(2) providing facts known to the examiner as to "why the rejection should be maintained". The request is not germane because the rejection is maintained in view of the text of the specification and publications and appellate decisions cited and discussed in the rejection of record and Applicant's arguments. Applicant suggests that the communication mailed 16 November 2007 had not "set out a *prima facie* case of [a] lack of [adequate] written description" because a factual basis must be established by evidence and reasoning to rebut a presumption that the specification's disclosure is adequate. The disclosure must establish Applicant's possession, at the time the disclosure was originally filed, of an invention defined in, e.g., claims 27, 31, and 36 a "proteolytically active" polypeptide that "consists essentially of an HCV NS3 domain protease" or "an active truncation analog" of an HCV NS3 domain protease", a fusion polypeptide comprising such a proteolytically active polypeptide, and an assay for detecting inhibitors of such a proteolytically active polypeptide.

Claims 30 and 35 provide a statement of what might consist essentially of an HCV NS3 domain protease: the 202 amino acid sequence identically set forth in both SEQ ID NO:1 and SEQ ID NO:65.<sup>1</sup> Neither the specification nor Applicant's argument assert that this 202 amino acid sequence is the least of "active" truncation analogs. Whether it is intended to be the least truncation or a starting point for truncation, the specification nowhere discloses that it is capable of proteolytically cleaving the only substrates purported to be cleaved by a HSV NS3 domain protease: the p300, p500, and p600 fusion constructs of Examples 4 and 5.<sup>2</sup> Alternatively, Examples 4 and 5 suggest that an HCV NS3 domain protease might consist of the 686 amino acid sequence set forth in SEQ ID NO:70. This is the greatest portion of the HSV polyprotein disclosed by the specification fused to human superoxide dismutase [HSOD] to provide the "P600" fusion polypeptide the amino acid sequence of which is set forth in SEQ ID NO:86.

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<sup>1</sup> The undecapeptide of SEQ ID NO:63 and the nonapeptide of SEQ ID NO:64 described by claims 28, 29, 33, and 34 are far too small to retain proteolytic activity. Both peptides reside within SEQ ID NO:65.

<sup>2</sup> The specification suggests, at pages 19-21, that peptides comprising at least two consecutive arginines, or the three particular peptides set forth in SEQ IDs NOs:36, 88, and 89, or the HCV polyprotein, are all potential substrates but does not disclose the structure of a HCV NS3 domain protease that cleaves at two consecutive arginines, cleaves the peptides set forth in SEQ IDs NOs:36, 88, and 89 or that can independently cleave any particular portion of the HCV polypeptide.

Applicant asserts at pages 6 and 9-15 of the Response that this particular, larger, structure, an entire NS3 domain, disclosed in the specification and comprising SEQ ID NO:65 may have an "NS2/NS3" proteolytic activity, but the specification does not contemplate such activity. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The NS2/NS3 autocatalytic metalloprotease activity takes place at a region of the HCV polyprotein that is absent from SEQ ID NO:70, a fact established by the record of argument in this application, and was discovered after the specification was originally filed, thus could not reasonably be considered by the artisan to have been in Applicant's possession at the time the specification was originally filed. Applicant also asserts at page 6 of the Response that an NS3 serine protease activity is disclosed in Examples 10 and 11 but neither discusses proteolysis or NS3 domain serine protease activity. The "test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the Inventor had possession at that time of the . . . claimed subject matter", *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983).

There are two factual inquiries presented regarding Applicant's assertion that an NS3 domain serine protease activity is adequately described by the disclosure of Examples 5 and 6 of the specification. Is there any disclosure that the structure defined by SEQ ID NO:65 meets the functional limitation of serine protease activity stated in claims 27, 31, and 36? If this structure does not, does the specification disclose some other, more extensive, structure adequate to reasonably convey to the artisan that Applicant had possession of a NS3 domain polypeptide with serine protease activity according to claims 27, 31, and 36? At pages 6-9 of the Response Applicant asserts that several publications made five or more years after the specification was originally filed indicate that that SEQ ID NO:65 might function, alone, as a serine protease, but only Lin et al., and Sardana et al., previously made of record by the examiner, are present in the record of this application and none of the HCV polyprotein regions that Sardana et al. report to be substrates cleaved by an HCV NS3 serine protease are disclosed or suggested in the specification and all are absent from the expression constructs of Examples 4 and 5. The portions of Vishnuvardhan et al. and Barbato et al., quoted in the Response do not suggest that SEQ ID NO:65 has a serine protease activity demonstrable with any region within the P300, P500, or P600 fusion polypeptides thus cannot compensate for the failure of the specification to disclose that any region of the HCV polyprotein that could serve as a substrate is present in any of the P300, P500, or P600 fusion polypeptides, purportedly cleaved, at least by SEQ ID NO:70,

in Example 5. The cleavage sites applicant cites at pages 7 and 8 of the Response upon which a NS3 domain protease might act without the assistance of the NS4A peptide subsequently identified by Lin et al., 1994, of record, Bartenschlager et al., 1994, and Bartenschlager et al., 1995, both made of record herewith, are not present in SEQ ID NO:70. Where none are present, even in the P600 construct, the specification cannot be considered to have disclosed Applicant's possession of a NS3 domain serine protease. An ancillary argument at pages 10 and 11 of the Response urges that the presence of HSOD as an amino-proximal fusion partner reconstitutes a kind of NS2/NS3 autocatalytic cleavage but this is unpersuasive because the mass of the cleavage fragment produced does not indicate that the cleavage was produced by a HCV NS2/3 autocatalytic activity and such proteolytic activity, when it occurs in a naturally-occurring HCV polyprotein, is not a serine protease activity. The rejection of record is therefore maintained.

Claims 27-36 remain rejected for reasons of record 35 U.S.C. § 112, first paragraph, because the specification does not reasonably provide enablement for preparing a protein of the claimed compositions and assay having HCV-specific protease activity, including the P600, P500, P300 or P190 proteins and generic versions or active truncation analogs thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

Applicant's arguments at pages 15-22 of the Response have been fully considered but are not persuasive. Applicant requests withdrawal of the rejection of record at pages 15 and 16 of the Response if the Declarations filed 12 October 2005 and 12 February 2007 are not persuasive. The Declarations were addressed in previous communications and the rejection is maintained in view of the publications, and the appellate decisions, cited in the body of the rejection. The Response first suggests, at pages 16-19, that the specification enables the preparation of a NS2/NS3 domain protease that might arise due to a fusion with superoxide dismutase. The specification, however, teaches away from the preparation of anything other than a serine protease and provides no guidance that could help the artisan select the portion of the NS2 domain that must be included to conduct an autocatalysis disclosed by others only after the application was filed. The Response then suggests at pages 19-21 that the specification discloses an adequate substrate, "in the form of [the] HCV polyprotein" with which experimentation might be conducted, and that its use "for testing NS3 serine protease activity in *trans*", might require no undue experimentation on the part of the artisan to make HCV NS3 domain proteases commensurate in scope with the recitations of the claims rejected herein. With regard to what may constitute "undue experimentation", the CCPA, the precursor of the Court of Appeals for the Federal Circuit, determined that a **reasonable correlation** must exist

between the **scope asserted** in the claimed subject matter and the **scope of the guidance** the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (emphasis supplied). The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997). Yet the teaching of the specification that the amino acid sequence of SEQ ID NO:65, the most particular embodiment described by claims 30 and 35, cannot be combined with the state of the art at the time the specification was filed to permit the preparation of a claimed protease, or the practice of an assay of claim 36 with a such a protease, by one of ordinary skill in the art at that time without undue experimentation. This is because, while SEQ ID NO:65 includes all residues necessary for NS3 domain serine protease cleavage at the NS5A/5B junction, it includes no amino acid sequence region that permits cleavage at the NS2/3 junction by a NS2/3 metalloprotease or cleavage at any of the NS3/4A, NS4A/4B or NS4B/5A junctions by a NS3 serine protease. The specification provides no guidance for the artisan to select the HCV NS5 domain as a substrate for serine protease activity. Indeed, the only substrates the specification proposes – see pages 19-21 of the specification as discussed in the preceding rejection – are not substrates of the NS3 domain serine protease of SEQ ID NO:65. Applicant argues at page 22 of the Response that the teaching of the amino acid sequence of SEQ ID NO:65 and the availability of an HCV polyprotein substrate would guide the artisan to prepare products that might populate the genera of proteases embraced by claims 27-35 rejected herein, and practice an assay of claim 36 with such generic products but there is no guidance in the specification as to what more might be required beyond the amino acid sequence of SEQ ID NO:65 to locate the sequence of NS4A cofactor, a region absent from SEQ ID NO:65 and discovered by others well after the date for the disclosure of the specification herein, that could bring about cleavage of the native polyprotein. Because the scope of guidance provided by the specification does not indicate the direction the artisan might take to begin the next, necessary, process of experimentation, the rejection of record is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-36 remain rejected for reasons of record under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant' arguments at pages 22-24 of the Response have been fully considered but are not persuasive. Applicant suggests that the artisan might be able to distinguish that which is infringed from that which is not infringed as long as a polypeptide (i) has some origin in a HCV

polyprotein and (ii) has protease activity. Yet the independent claims 27, 31, and 36 provide no basis for the artisan to distinguish between a “HCV NS3 domain protease” and a “truncation analog” of a HCV NS3 domain protease that is proteolytically active. It is agreed that “functional language”, if it is itself definite, “does not in and of itself, render a claim improper” but claims 27-36 rejected herein lack both a particular function and a basis for measuring what might provide some function. There is no starting point that allows any distinction to be made, other than an entire HCV polyprotein, thus the Response seems to argue that any polynucleotide encoding all or part of an HCV polyprotein, and any polynucleotide derived from the HCV viral genome but differing to an indeterminable extent from a disclosed HCV nucleic acid sequence, should be considered by the artisan to be the invention, if it can be altered to have a protease activity. Where there is no starting point delineating a structure that permits the artisan and the public to distinguish between polynucleotides that need have no particular relationship to a disclosed polynucleotide and that encode any kind of protease that will cleave HCV polyproteins anywhere, whether or not the site is actually recognized by a native HCV NS3 domain serine protease, the metes and bounds of the intended subject matter are clearly indefinite. Until and unless the claims are amended to provide a definite basis for distinguishing a first “HCV NS3 domain protease”, and all lesser truncation analogs, from other proteases, the rejection of record of claims 27-36 must sustained.

#### *Conclusion*

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr Bragdon, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

/William W. Moore/  
5 August 2008

/  
Kathleen Kerr Bragdon  
Supervisory Primary Examiner  
Art Unit 1656